IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: **Stamm et al**

Application No. **10/288,425** Group Art Unit: **1615**

Filed: **November 6, 2002** Examiner: **H. Sheikh**

For: **FENOFIBRATE PHARMACEUTICAL COMPOSITION HAVING HIGH BIOAVAILABILITY AND METHOD FOR PREPARING IT**

Attorney Docket No: 107664.115US6

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Declaration under 37 C.F.R. § 1.132

I, Philippe Réginault, declare as follows.

1. I am a 1973 graduate of the INA in France.

2. I have been employed by Laboratoires Fournier, the assignee of the above-identified application, since 1981. I successively held the following positions within Laboratoires Fournier:

- 1981-1985: Head of section "Research of Natural Products" (Selection of plants for extraction and search for biologically active substances).
- 1985-1988: Vice-manager of Bio formulation.
- 1988-2002: Director of Pharmaceutical Development (in charge of Formulation, Scale up, Analytical Development, CMC section and Clinical Supplies).
- 2002-Present: Director of Pharmaceutical Technologies Evaluation.

3. I have been named in the following publications, including patents (original French titles): process for preparing a therapeutically useful extract from Brackenridgea zanguebarica, extract and such a medicine (EP 0126691); self-adhesive device for transdermal administration of an active agent (U.S. Patent Nos. 4,842,864 and 4,837,025); treatment of impotence (US Patent No. 5,451,609); treatment of acute urinary retention (US Patent No. 5,561,154); Update in theophylline therapy : monodisperse spherical microbeads permitting user's self dosage adjustment; B. Curtet; M. Lamoise; P. Réginault; E. Teillaud; Poster 15th International Symposium on Controlled Release of Biomaterials. 1988; Cellules à flux

continu: exemples d'application aux microsphères, à différents pH; B. Curtet; M. Lamoise; P. Réginault; E. Teillaud; S.T.P. Pharma (1990), 6(9), 673-7; Micronized fenofibrate; J.P. Guichard; A. Munoz; P. Réginault; Atherosclerosis (1994), 110, S45-S48; Assessing the particle size of a broadly dispersed powder by complementary techniques; C. Andrès; P. Bracconi; P. Réginault; P. Blouquin; M.H. Rochat; Y. Pourcelot; International Journal of Pharmaceutics 167, (1998), 129-138.

4. I am a co-inventor of U.S. Patent No. 4,895,726 (the Curtet reference), which has been cited by the U.S. Patent Office to reject the claims in the above-identified application.

5. I have read and understood PCT/IB98/00065, and the U.S. Application Nos. 09/899,026 and 10/288,425 (i.e., the above-identified application).

6. I have read and understood U.S. Patent No. 4,800,079 (the Boyer reference).

7. To the best of my knowledge, the product Lipanthyl® 250 (manufactured by Ethypharm and marketed by Laboratoires Fournier) is manufactured in accordance with the teachings in U.S. Patent No. 4,800,079 (the Boyer reference). Lipanthyl® 250 contains 250 mg of fenofibrate is manufactured as a capsule containing microgranules. In the following Tables and Figures, Lipanthyl® 250 is identified as batch 70825.

8. To the best of my knowledge, the product Lipanthyl® Supra (manufactured and marketed by Laboratoires Fournier) is manufactured in accordance with the teachings in PCT/IB98/00065 and the above-identified application. Lipanthyl® Supra contains 160 mg of fenofibrate and is manufactured as a tablet. In the following Tables and Figures, Lipanthyl® Supra is identified as batch 72197.

9. I supervised dissolution tests where the dissolution was determined using a paddle apparatus, USP type 2. The paddle speed was 75 rpm. The dissolution medium was 1.00 L of 0.025 M aqueous sodium laurylsulfate at 37 ± 0.5°C.

10. For the test, six units (i.e., tablets or capsules) were tested. In order to exclude the lag time due to the capsule opening for Lipanthyl® 250, the microgranules contained in each capsule were used as the test samples. The dissolution medium was sampled at 5, 10, 20, 30 and 60 minutes. The fenofibrate concentration in the dissolution medium samples was determined by ultra-violet spectrophotometry at the maximum absorbance wavelength of fenofibrate.

11. The results are given in the following Tables 1 and 2, where the amounts of fenofibrate dissolved in the medium are expressed either as % of the label strength or as mg fenofibrate dissolved. Figures 1 and 2 below are a graphical representation of the numerical results found in Tables 1 and 2, respectively.

Table 1: Dissolution of Lipanthyl® Supra Corresponding to Claims in US Application No. 10/288,425

Time (min)	Unit dose 1	2	3	4	5	6	Mean	SD	RSD %
% dissolved									
5	33.0	31.9	26.5	18.6	26.1	24.5	26.8	5.2	19.6
10	65.2	63.2	61.5	51.8	61.8	59.5	60.5	4.7	7.7
20	82.6	82.3	83.9	83.8	83.4	81.7	83.0	0.9	1.1
30	89.4	89.6	89.7	92.5	89.6	88.3	89.8	1.4	1.5
60	94.8	95.2	96.2	99.4	94.7	94.2	95.7	1.9	2.0
mg dissolved									
5	52.8	51.1	42.4	29.7	41.8	39.2	43	8.40	19.6
10	104.3	101.1	98.4	82.9	98.9	95.2	97	7.46	7.7
20	132.2	131.7	134.3	134.1	133.4	130.8	133	1.40	1.1
30	143.0	143.4	143.6	147.9	143.3	141.4	144	2.20	1.5
60	151.7	152.3	154.0	159.0	151.6	150.7	153	3.05	2.0

Table 2: Dissolution of Lipanthyl® 250 Corresponding to U.S. Patent No. 4,800,079 to Boyer

Time (min)	Unit dose 1	2	3	4	5	6	Mean	SD	RSD %
% dissolved									
5	0.3	0.4	0.3	0.3	0.3	0.3	0.4	0.0	9.8
10	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.0	0.0
20	1.2	1.2	1.2	1.2	1.2	1.3	1.2	0.0	2.9
30	1.8	1.8	1.9	1.9	1.9	2.0	1.9	0.1	3.4
60	3.9	4.0	4.0	4.0	3.9	4.6	4.0	0.3	6.5
mg dissolved									
5	0.9	1.1	0.9	0.9	0.9	0.9	0.9	0.1	9.8
10	1.5	1.5	1.5	1.5	1.5	1.5	1.5	0.0	0.0
20	3.0	3.0	3.0	3.0	3.0	3.2	3.1	0.1	2.9
30	4.5	4.5	4.7	4.7	4.7	5.0	4.7	0.2	3.4
60	9.7	9.9	9.9	9.9	9.7	11.4	10.1	0.7	6.5

Figure 1

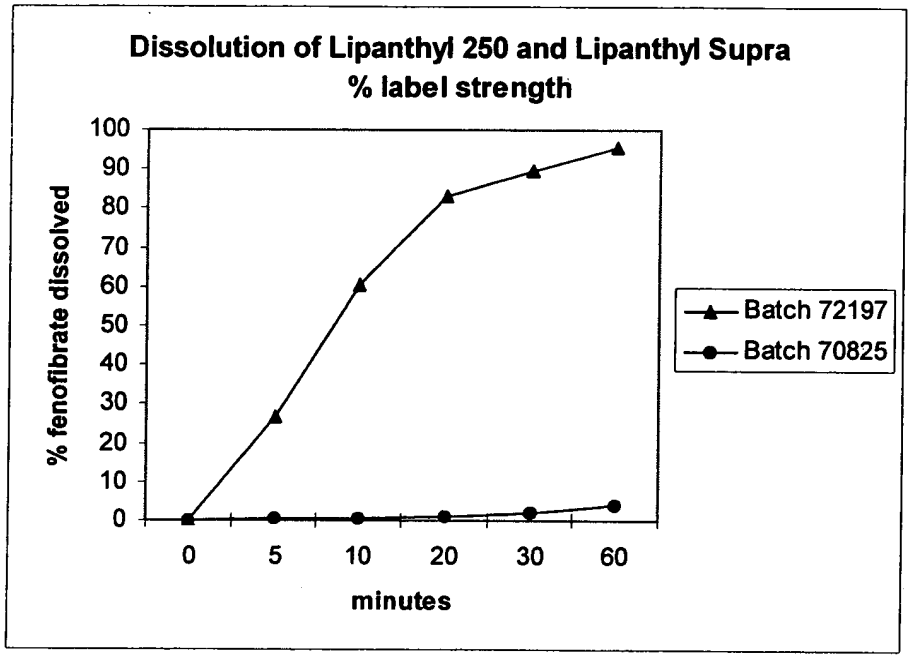
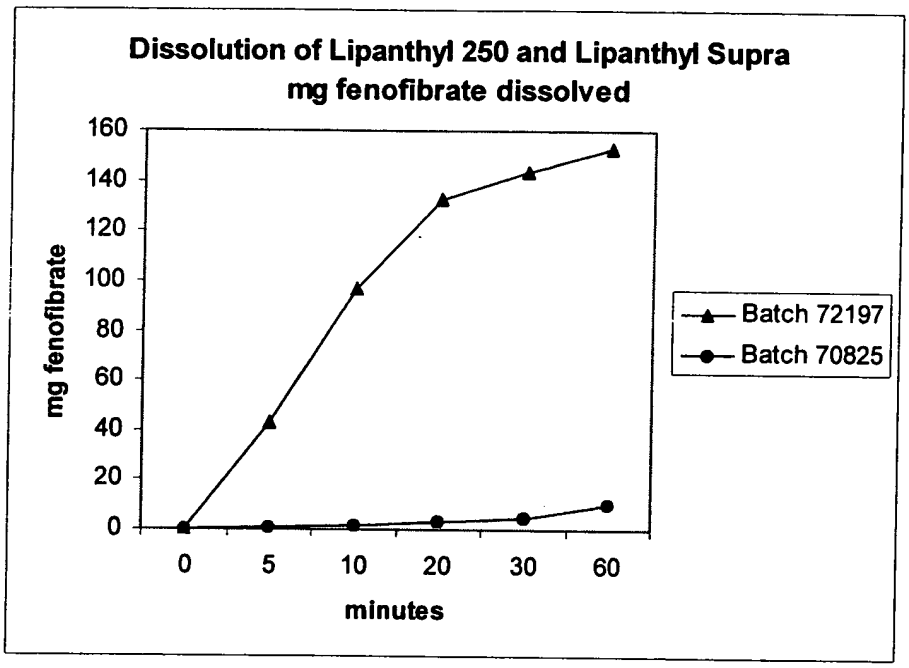

Dissolution of Lipanthyl 250 and Lipanthyl Supra
% label strength
% fenofibrate dissolved
100
90
80
70
60
50
40
30
20
10
0
0
5
10
20
30
60
minutes
Batch 72197
Batch 70825

Figure 2



12. The results shown above clearly demonstrate that Lipanthyl® 250 (i.e., U.S. Patent No. 4,800,079 to Boyer) and Lipanthyl® Supra (i.e., the above-identified application) have very different dissolution profiles — both for the extent and for the rate. Lipanthyl® Supra presented a complete dissolution of fenofibrate within 1 hour whereas Lipanthyl® 250 only released 4% fenofibrate (i.e., 10 mg) within 1 hour.

13. It is my opinion that the claimed invention has a superior dissolution profile when compared to the dissolution profile of U.S. Patent No. 4,800,079 to Boyer.

14. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity or enforceability of the present application or any patent issued thereon.

Philippe Régimbault

June 16th, 2003
Date